Clinical efficacy of avapritinib in gastrointestinal stromal tumors (GISTs) with different *KIT* genotypes: post hoc analysis of the phase 1 NAVIGATOR and phase 1/2 CS3007-101 trials

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Abstract #11523

BACKGROUND

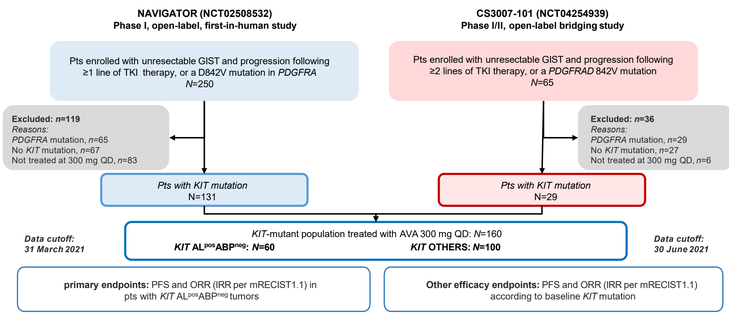
- Tyrosine kinase inhibitors targeting KIT/PDGFRA are the standard of care for patients with unresectable/metastatic GISTs. However, the efficacy of approved tyrosine kinase inhibitors (TKIs) for GISTs is modest and varies according to genotypes in the second- and later-line settings.[1,2] A tumor-genotype-based treatment paradigm is needed.
- Avapritinib (AVA) is a highly selective KIT/PDGFRA inhibitor approved to treat patients (pts) with *PDGFRA18*-mutant GISTs that has also demonstrated preclinical activity against *KIT* activation loop (AL) and *KIT exon 9* (*KIT* 9) mutations.[1,3]
- A post hoc efficacy analysis of AVA in pts with non-*PDGFRA*-mutant GISTs enrolled in the phase 1 NAVIGATOR (NCT02508532) and phase 1/2 China bridging (NCT04254939; CS3007-101) trials[4,5] was conducted.

METHODS

Study design and patients

- Pts with *KIT* mutations treated with 300 mg QD AVA from either trial were included in the analysis. Tumor tissue and/or plasma (circulating tumor DNA) were analyzed at baseline to identify tumor *KIT* mutations.
- Pts were divided into two groups: those with *KIT* AL (exon 17 or 18) mutations without *KIT* ATP binding pocket (ABP; exon 13 or 14) mutations (*KIT* AL^{pos}ABP^{neg}) versus all other *KIT* mutations (*KIT* OTHERS) (**Figure 1**).
- Progression-free survival (PFS) and objective response rate (ORR) were compared using Cox and logistic regression, respectively; adjustment by inverse probability weighting of baseline characteristics (IPW$_{BL}$) was conducted.

Figure 1. Pt population for the post-hoc analysis of AVA in *KIT*-mutant GIST



GIST, gastrointestinal stromal tumor; IRR, independent radiology review; *KIT* AL^{pos}ABP^{neg}, activation-loop positive, ATP binding pocket negative; mRECIST1.1, modified Response Evaluation Criteria in Solid Tumors version 1.1; ORR, objective response rate; PFS, progression-free survival; pts, patients; QD, once daily.

RESULTS

Patient population

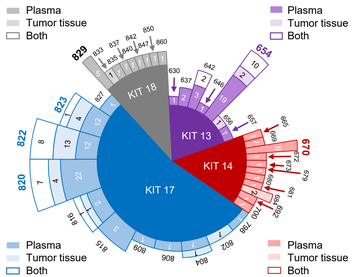
- The pts were predominantly male (63.8%) and White (56.9%) with heavily treated (61.3% with ≥3 prior TKIs) metastatic disease (96.9%) (**Table 1**).
- *KIT*-AL mutations occurred more frequently than *KIT*-ABP mutations (**Table 1**, **Figure 2**).
- Median follow-up duration was 22.0 months (range, 0.5–39.0 months).

Table 1. Pt demographic and baseline characteristics

n (%) unless stated otherwise	All patients (*N*=160)
Age (years), median (range)	58 (33–80)
Sex, male	102 (63.8%)
Ethnicity	
White	91 (56.9)
Asian	45 (28.1)
Other	24 (15.0)
Tumor size (longest diameter), cm	
≤5	59 (36.9)
>5 to 10	71 (44.4)
>10	26 (16.3)
Missing	4 (2.5)
Metastatic disease, yes	155 (96.9)
Location of KIT mutation	
ECD exon 9	43 (26.9)
JMD exon 11	111 (69.4)
AL exon 17/18	74 (46.3)
ABP exon 13/14	34 (21.3)
AL^{pos}ABP^{neg}	60 (37.5)
≥3 prior TKIs	98 (61.3)

AL, activation loop; AL^{pos}ABP^{neg}, activation-loop positive, ATP binding pocket negative; ABP, ATP binding pocket; ECD, extracellular domain; JMD, juxtamembrane domain.

Figure 2. Distribution of *KIT* AL and ABP mutations



Label number outside the sector diagram represents the affected codon in KIT; Label number in the sector represents the number of patients with corresponding mutations detected. ABP, ATP binding pocket; AL, activation loop; TISSUE, tumor tissue

Antitumor response

- The unadjusted ORR was significantly higher in the *KIT* AL^{pos}ABP^{neg} group than in the *KIT* OTHERS group (26.7% [16/60] vs 12.0% [12/100]; P=0.0185); the disease control rate was also higher (**Table 2. Figure 3**); findings were consistent following IPW$_{BL}$ adjustment (ORR, 31.4% vs 12.1%; P=0.0047).
- Pts receiving AVA in the 2L setting (38.5%) achieved numerically higher ORRs compared with those receiving other lines (**Table 2**).
- ORRs were numerically higher for Chinese pts (36.4%) than for non-Chinese pts (24.5%) in the ≥2L setting (P=0.4244) (**Table 2**).
- Meaningful antitumor activity was seen in pts with *KIT*-9-mutant GIST in the fourth- and later-line (≥4L) settings (**Table 2**).

Table 2. Tumor response data

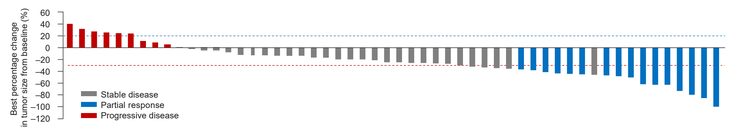
Data are n (%) unless stated otherwise	*KIT* groups: unadjusted		*KIT* groups IPW$_{BL}$-adjusted		Efficacy in *KIT* AL^{pos}ABP^{neg} by therapy line				*KIT* AL^{pos}ABP^{neg} (≥2L)		*KIT* 9	
	AL^{pos}ABP^{neg}	OTHERS	AL^{pos}ABP^{neg}	OTHERS	2L	3L	4L	>4L	Chinese	Non-Chinese	4L	>4L
	N=60	*N*=100	*N*=58	*N*=95	*n*=13	*n*=9	*n*=15	*n*=23	*n*=11[b]	*n*=49[c]	*n*=14	*n*=19
ORR (%)	**26.7**	**12.0**	**31.4**	**12.1**	**38.5**	**22.2**	**20.0**	**26.1**	**36.4**	**24.5**	**14.3**	**15.8**
Partial response	16 (26.7)	12 (12.0)	31.4	12.1	5 (38.5)	2 (22.2)	3 (20.0)	6 (26.1)	4 (36.4)	12 (24.5)	2 (14.3)	3 (15.8)
Stable disease	30 (50.0)	43 (43.0)	47.2	43.6	6 (46.2)	6 (66.7)	9 (60.0)	9 (39.1)	6 (54.5)	24 (49.0)	9 (64.3)	10 (52.6)
Progressive disease	10 (16.7)	40 (40.0)	15.8	40.5	2 (15.4)	1 (11.1)	3 (20.0)	4 (17.4)	0	10 (20.4)	3 (21.4)	6 (31.6)
Not available/unknown	4 (6.7)	5 (5.0)	5.7	3.8	0	0	0	4 (17.4)	1 (9.1)	3 (6.1)	0	0
Odds ratio (95%CI), %	2.67 (1.16–6.12)		3.31 (1.44–7.58)		–	–	–	–	1.76 (0.44–7.08)		–	
P value	0.0185		0.0047		–	–	–	–	0.4244		–	–
Disease control rate, n (%)	79.7	55.0	78.6	55.7	84.6	88.9	80.0	65.2	90.9	73.5	78.6	68.4

≥2L, second line and beyond; 2L, second line; 3L, third line; 4L, fourth line; >4L, beyond fourth line; AL^{pos}ABP^{neg}, activation-loop positive, ATP binding pocket negative; IPW$_{BL}$, inverse probability weighting of baseline characteristics; ORR, objective response rate.

CONCLUSIONS

- AVA demonstrated greater antitumor activity in pts with GIST harboring *KIT* AL^{pos}ABP^{neg} mutations than in pts with other *KIT* mutations.
- AVA is a promising 2L treatment option for pts with *KIT* AL^{pos}ABP^{neg}-mutant GISTs and has potential as a later-line therapy (≥ 4L) for pts with *KIT* 9 mutations.
- AVA may confer meaningful clinical benefit in pts with GIST and specific types of *KIT* mutation, especially *KIT*-AL or *KIT* 9 mutations.

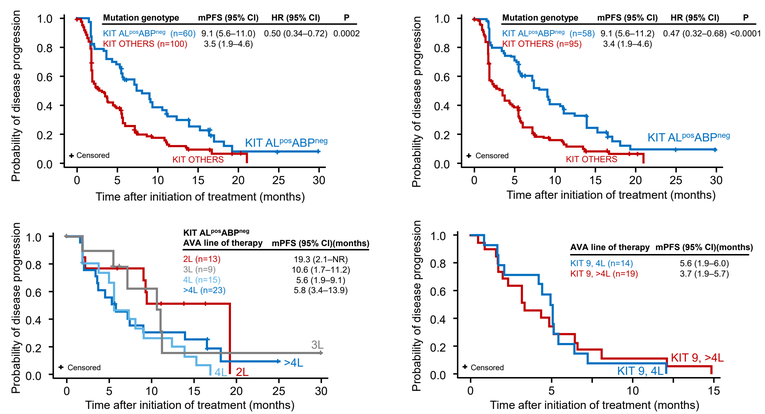
Figure 3. Best percentage change from baseline in tumor size: *KIT* AL^{pos}ABP^{neg} group



Progression-free survival

- Both unadjusted and IPW$_{BL}$-adjusted median PFS were significantly higher in the *KIT* AL^{pos}ABP^{neg} group versus *KIT* OTHERS (**Figure 4A,B**).
- A PFS benefit with AVA was observed in *KIT* AL^{pos}ABP^{neg} pts in the second-line setting over later lines (**Figure 4C**).
- There was also clinically meaningful PFS benefit with AVA in pts with a *KIT* 9 mutation in both the fourth-line (4L) and ≥4L settings (**Figure 4D**); median PFS was 7.2 months in *KIT* AL^{pos}ABP^{neg} pts harboring a *KIT* 9 mutation (*n*=8) in the 4L and ≥4L settings.

Figure 4. Kaplan–Meier estimates of PFS assessed by IRR per mRECIST (A) unadjusted and (B) after IPW$_{BL}$ adjustment, and by line of therapy (C) and in 4L and ≥4L pts with *KIT*-9-mutant disease (D)



2L, second line; 3L, third line; 4L, fourth line; >4L, beyond fourth line; AL^{pos}ABP^{neg}, activation-loop positive, ATP binding pocket negative; AVA, avapritinib; CI, confidence interval; HR, hazard ratio; mPFS, median progression-free survival.

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